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The optimization of a one-pot heteroconjugate addition-oxidation-diels-alder reaction

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The Optimization of a One-Pot Heteroconjugate Addition-Oxidation-Diels–Alder Reaction

by

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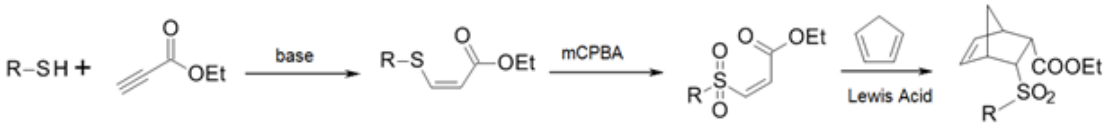
Table of Contents

Acknowledgments

All work was conducted under Dr. C. Wade Downey at the University of Richmond Chemistry Department. Members of the Downey group contributing to the previous work performed on this project were Brian Southall, ’08, Eric W. Etchill, ’08, Stephanie Corsi, ’09, and Smaranda Craciun, ’11. The work presented was also conducted in conjunction with Ana Neferu, ’13. Funding for this work was provided by grants from the American Chemical Society-Petroleum Research Fund and Thomas F. and Kate Miller Jeffress Memorial Trust and summer research fellowships from the University of Richmond School of Arts & Sciences, including the Howard Hughes Medical Institute.

Abstract

Ynoate esters are ideal reagents for one-pot reactions due to their ability to undergo multiple addition reactions in one flask. Ethyl propiolate undergoes a heteroconjugate addition reaction with aromatic thiol nucleophiles, producing an enoate which is then oxidized by *m*-CPBA and is able to undergo a Diels–Alder reaction with cyclopentadiene. The work presents the optimization of a three-step heteroconjugate addition-oxidation-Diels–Alder reaction to yield cyclic compounds favoring endo stereochemistry, which may be used in further synthesis of biologically active compounds such as (+)-Methyl-5-epi-Shikimate or Deipeptyl-IV-Peptidase inhibitor.



1. Background and Introduction

1.1. Introduction

One-pot synthesis methods are valuable in the production of molecules requiring multi-step synthesis, in which the product of each step of the reaction serves as the reagent in the following step of the synthesis. One-pot reactions save time and resources, with the efficiency of completing a multi-step synthesis in one flask, and by bypassing intermediate purification processes. Therefore, one-pot synthesis reactions would be a valuable tool for pharmaceutical companies in the production of complex pharmaceutical compounds.[1]

Furthermore, it has been established that ynoate acceptors serve as promising reagents in one-pot reactions due to their ability to participate in addition reactions with various nucleophiles.[2] Often, such addition reactions produce molecules favoring one geometric isomer of enoate, as shown in Figure 1. It has also been shown that thiol nucleophiles will favor either the *Z* or *E* isomer under different reaction conditions.[3,4]

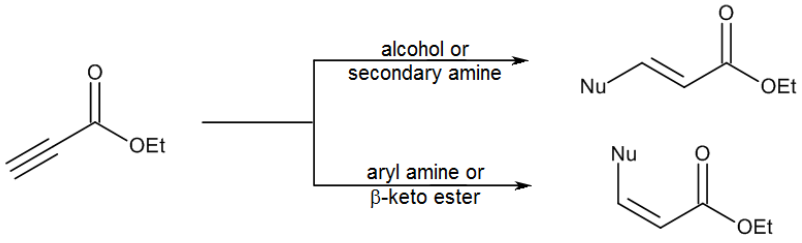
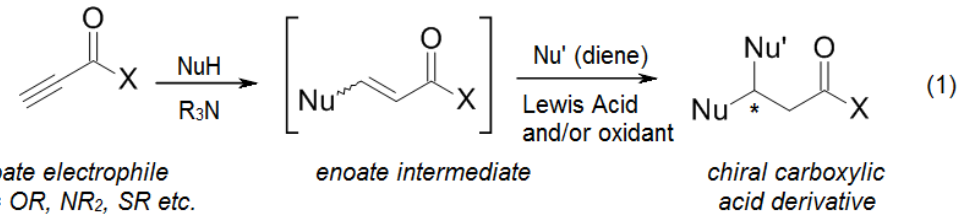


Figure 1. Stereoselective Synthesis of *Z* and *E* Enoates.

In addition, in the ring-forming Diels–Alder reaction, the dienophile will add to the diene with conserved stereochemistry, suggesting that compounds with a high *Z* to *E* isomer ratio would be useful in the completion of a stereoselective Diels–Alder reaction. Therefore, the stereoselectivity for the *Z* or *E* isomer in the addition of the nucleophile to

the ynoate acceptor will later affect the yield of specific stereoisomers of the Diels–Alder reaction.

With this knowledge, our goal has been to optimize a one-pot three-step heteroconjugate addition-oxidation-Diels–Alder reaction by first obtaining a high *Z* to *E* isomer ratio of the addition product, the enoate. Oxidation of the enoate and the addition of a Lewis acid, $LiClO_4$, then activates the enoate, creating an electrophile capable of completing a Diels–Alder cycloaddition favoring endo stereochemistry. The general scheme for this three-step one-pot synthesis is shown in Equation 1. Optimization of this one-pot reaction thus presents a valuable synthetic method due to the efficiency of the one-pot process and the ability to construct complex cyclic molecules for further use in pharmaceutical synthesis and development.



1.2 Proposed Mechanism:

The proposed mechanism for our optimized one-pot process is shown in Figure 2. A trialkylamine base deprotonates the thiol nucleophile, producing the thiolate anion and trialkylammonium cation. The thiol nucleophile then participates in the addition to the ynoate acceptor, resulting in the formation of the enoate ester product. The stereoselectivity of this step in the reaction sequence will then determine the amount of product participating in the Diels–Alder cycloaddition with the diene. However, the sulfur atom's position next to the enoate π system makes this dienophile too electron-rich to successfully participate in the Diels-Alder reaction. Thus, the sulfur atom must first be

oxidized before the addition of the diene to increase its electrophilicity before the addition of the diene. Because there are four stereocenters in the product, and often only a single stereoisomer is desired when performing synthesis, our ultimate goal is to gain the ability to control the stereochemistry of the final product with a chiral catalyst.[5]

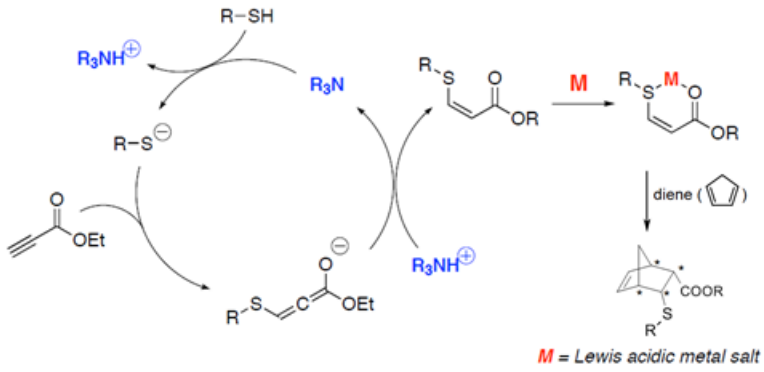


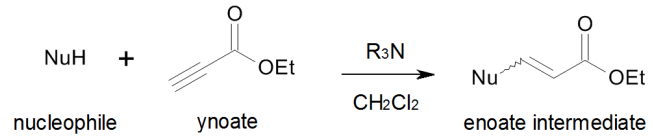
Figure 2. Proposed Mechanism for the One-pot Synthesis Reaction.

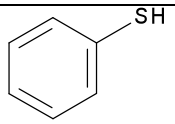
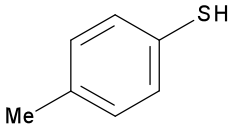
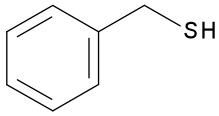
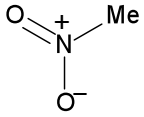
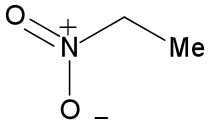
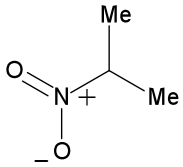
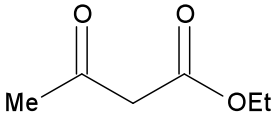
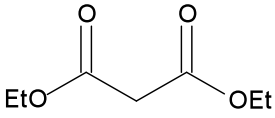
1.3 Previous Work:[i]

Previous University of Richmond students established the selectivity of various nucleophiles in a conjugate addition reaction to ethyl propiolate, which acts as an ynoate electrophile. The results shown in Table 1 illustrate that aromatic thiol nucleophiles yield the highest selectivity for the *Z*-isomer. Thus, aromatic thiols, such as *p*-toluenethiol, were chosen for future optimization studies.

[i] The experimentation with thiol nucleophile addition was performed by Brian C. Southall, and the results for addition with carbon nucleophiles were obtained by Eric. W. Etchill. Additional previous work on this project was performed by Stephanie Corsi and Smaranda Craciun.

Table 1. Addition of Various Nucleophiles to Ethyl Propiolate.

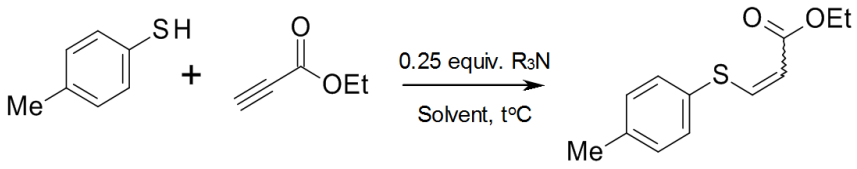


Nucleophile	R_3N	Temp.	*Z:E* Ratio	Conversion (%)
	i-Pr_2NEt	-78°C	12:1	100
	i-Pr_2NEt	-78°C	11:1	100
	i-Pr_2NEt	-78°C	4:1	100
	Et_3N	-42°C	3.5:1	99
	Et_3N	-42°C	2.5:1	30
	Et_3N	-42°C	2:1	20
	Et_3N	-42°C	2:1	30
	Et_3N	-42°C	6.5:1	85

Using *p*-toluenethiol as the model nucleophile, reaction conditions were optimized for the conjugate addition reaction through experimentation with a variety of solvents, catalytic amine bases, and temperatures. Table 2 demonstrates that the best

stereoselectivity and highest conversion were achieved with the conditions of methylene chloride as solvent, diisopropylethylamine as base, and -78 °C for the temperature of the conjugate addition reaction. Two additional thiol nucleophiles, benzylmercaptan and thiophenol, were used as nucleophiles in the addition reaction under the optimized conditions, and yields ranged from 94-99% with selectivity for the *Z*-isomer.[6] Thus, it was established that aromatic thiol nucleophiles are ideal candidates for the first step of conjugate addition in the full one-pot sequence.

Table 2. Optimization of Reaction Conditions for the Heteroconjugate Addition of *p*-toluenethiol to Ethyl Propiolate.



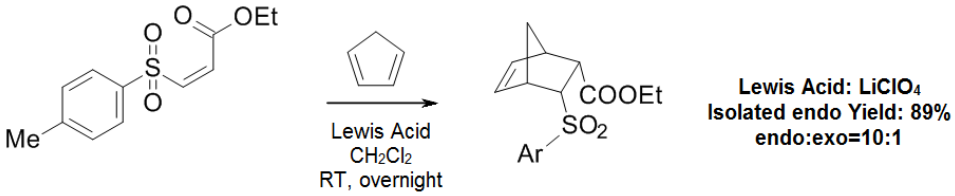
Solvent	Temp.	R_3N	*Z:E*	Conversion
$CHCl_3$	RT	*i*-Pr_2NEt	2.50:1	90%
EtOAc	RT	*i*-Pr_2NEt	2.00:1	100%
THF	RT	*i*-Pr_2NEt	2.00:1	90%
Et_2O	RT	*i*-Pr_2NEt	1.50:1	100%
Toluene	RT	*i*-Pr_2NEt	1.50:1	100%
CH_2Cl_2	RT	*i*-Pr_2NEt	3.00:1	100%
CH_2Cl_2	0°C	*i*-Pr_2NEt	3.77:1	100%
CH_2Cl_2	**-78°C**	***i*-Pr_2NEt**	**10.8:1**	**100%**
CH_2Cl_2	-78°C	Et_3N	10.3:1	92%
CH_2Cl_2	-78°C	2,6-Lutidine	12.0:1	90%

Furthermore, the ultimate goal of the one-pot sequence is to produce cyclic compounds through the completion of a Diels–Alder reaction. However, the enoate esters resulting from the conjugate addition reaction are too electron rich to undergo Diels–Alder reactions successfully. Therefore, experiments were conducted to optimize

the oxidation of the enoate esters, and it was found that meta-chloroperbenzoic acid (*m*-CPBA) oxidizes the sulfur atom of the enoate esters to yield β-sulfoxides and β-sulfones, depending on the stoichiometry of *m*-CPBA added. An excess of *m*-CPBA (greater than 2 equivalents) yields β-sulfones that retain stereoselectivity in favor of the *Z*-isomer and undergo Diels–Alder reactions with cyclopentadiene, as shown in previous work.[6]

After optimizing the conjugate addition conditions and establishing oxidation of the resulting thioethers, work in the Downey group then established the use of $LiClO_4$ as a Lewis acid to aid in the addition of cyclopentadiene to the β-sulfone in a Diels–Alder reaction. The results shown in Table 3 establish that the use of $LiClO_4$ yields Diels–Alder cycloaddition products with the greatest endo to exo selectivity using *p*-toluenethiol as the model nucleophile. Thus, previous efforts established the standard reaction conditions for the one-pot synthesis.

Table 3. Optimization of the Diels–Alder Cycloaddition of Cyclopentadiene to *p*-toluenethiol β-sulfone.



Lewis Acid	endo:exo[a]	Conversion[a]
$LiClO_4$	**10.1:1**	**99%**
$Zn(OTf)_2$	2.2:1	97% [b]
$MgBr_2{\cdot}OEt_2$	3.3:1	99%
$MgBr_2{\cdot}OEt_2$	2.3:1	77% [b]
$NaSbF_6$	2.4:1	76% [b]
$ZnBr_2$	5.7:1	37%
$Sn(OTf)_2$	3.7:1	29%
$Yb(OTf)_3$	3.1:1	24%
$In(OTf)_3$	3.7:1	27%

[a]Determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.
[b]Reaction carried in the presence of (–)-N-methylephedrine and *i*-Pr_2NEt.

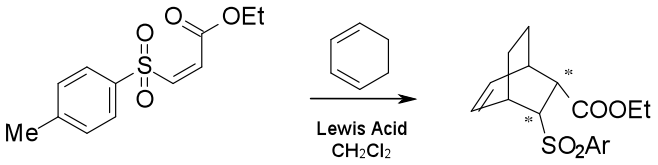
2. Results and Discussion:[ii]

In an attempt to increase the variety of dienes to be used in the Diels–Alder reaction of the one-pot sequence, a multitude of different dienes was investigated along with a variety of different Lewis acids. Dienes that were investigated included thiophene, 2-methylthiophene, 1-methylpyrrole, furan, isoprene, and cyclohexadiene. Cyclohexadiene was the only diene to show potential for successful conversion to the Diels–Alder product, and optimization of reaction conditions was investigated. Table 4 illustrates the finding that $LiClO_4$ was the only Lewis acid found to yield any conversion to the Diels–Alder product for the addition of cyclohexadiene to the β-sulfone derived

[ii] Results presented in this section were obtained in conjunction with work performed by Smaranda Craciun and Ana Neferu.

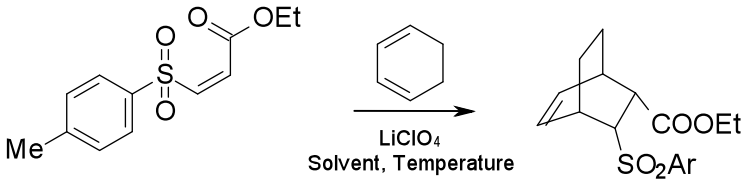
from *p*-toluenethiol, as analyzed by NMR. Solvent and temperature conditions with $LiClO_4$ were also investigated, as shown in Table 5, and it was determined that CH_2Cl_2 was the only successful solvent.

Table 4. Lewis Acid Optimization of Diels–Alder Cycloaddition of Cyclohexadiene to *p*-Toluenethiol Sulfone.



Lewis Acid	Conversion (%)
$LiClO_4$	80
$ZnBr_2$	0
$MgBr_2 \cdot OEt_2$	0
$NaSbF_6$	0
$Yb(OTf)_3$	0
$In(OTf)_3$	0

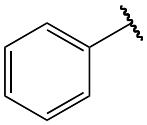
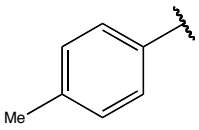
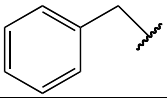
Table 5. Solvent and Temperature Optimization of Diels–Alder Cycloaddition of Cyclohexadiene to *p*-Toluenethiol Sulfone with $LiClO_4$ as a Catalyst.



Solvent	Temperature (°C)	Conversion (%)
CH_2Cl_2	50	80
$CHCl_3$	63	0
Benzene	80	0
Toluene	80	0
THF	65	0

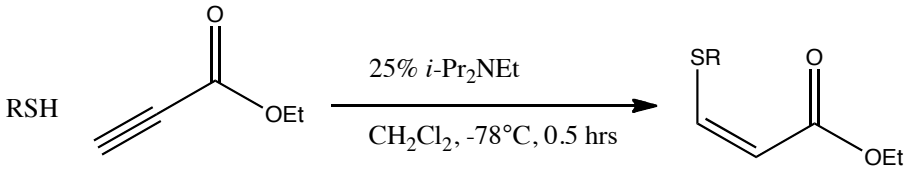
Finally, conversions were obtained for the cycloaddition of cyclohexadiene to the β-sulfones derived from the three previously investigated thiols (thiophenol, *p*-toluenethiol, and benzylmercaptan), shown in Table 6.

Table 6. Results for Optimized Diels–Alder Cycloaddition Conditions of Cyclohexadiene to Various Aromatic Sulfones.

R	Conversion (%)
	30
	50
	80

The maximum isolated yield for the Diels–Alder reaction of cyclohexadiene was disappointing (less than 30%), despite what appeared to be high conversion by NMR in some cases. After obtaining less successful results for the Diels–Alder step of the one-pot sequence with cyclohexadiene than with cyclopentadiene, it was concluded that cyclopentadiene held more promise for future studies of the one-pot process. Therefore, no further yields or characterization data were obtained for the products synthesized in Table 6 and research was focused on the conjugate addition of different thiol nucleophiles to ethyl propiolate, shown in Table 7. The previously optimized conditions were used for all addition reactions.

Table 7. Additional Conjugate Addition Reactions.



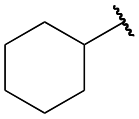
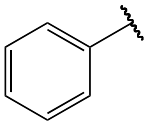
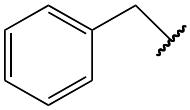
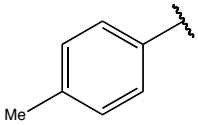
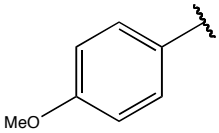
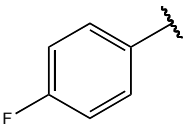
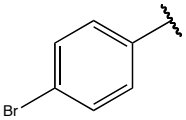
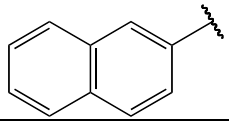
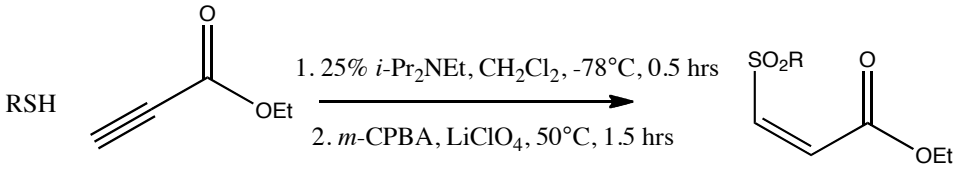
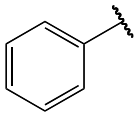
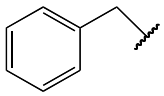
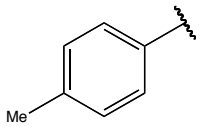
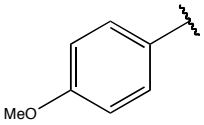
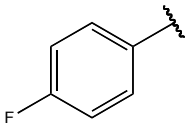
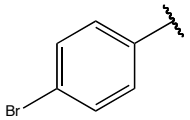
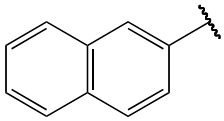
Thiol	*Z:E*	Yield % (*Z*+*E*)	Product
	6:1	67	1a
	12:1	94	1b
	5:1	96	1c
	10:1	99	1d
	15:1	95	1e
	6:1	97	1f
	8:1	86	1g
	11:1	91	1h

Table 8. Additional One-Pot Conjugate Addition-Oxidation Reactions.



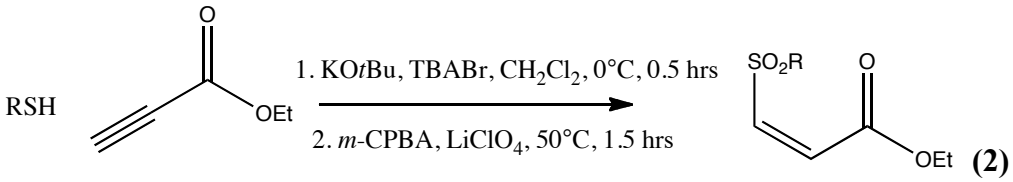
Thiol	*Z:E*	Yield % (*Z*)	Product
	12:1	77 (*Z*+*E*)	2b
	5:1	77 (*Z*+*E*)	2c
	8:1	91 (*Z*+*E*)	2d
	10:1	90	2e
	10:1	70	2f
	3:1	51*	2g
	10.1	84	2h

*Dichloroethane used as solvent.

As is evident from the comparison of the ratio of *Z* to *E* isomers after the first addition step of the one pot sequence with the conjugate addition-oxidation one-pot sequence, the ratio of *Z* to *E* decreases as the one-pot reaction sequence progresses. This is likely due to the ultimate isomerization of the *Z* isomer to the *E* isomer due to attack at the double bond of the enoate by a nucleophile in the reaction mixture, resulting in a

single bond with the ability to rotate and isomerize to the more stable *E* configuration. The rate of isomerization occurs more quickly with the presence of an electron withdrawing group substituent on the aromatic ring.

In addition, decomposition was observed for the cyclohexane thiol nucleophile under normal oxidation conditions, and other members of the Downey group were able to determine an alternative procedure to synthesize the cyclohexane thiol sulfone, illustrated in Equation 2. A stronger catalytic base is necessary to deprotonate an active amount of the thiol nucleophile in these cases, and the tetrabutylammonium additive is necessary to increase the solubility of the nascent thiolate.

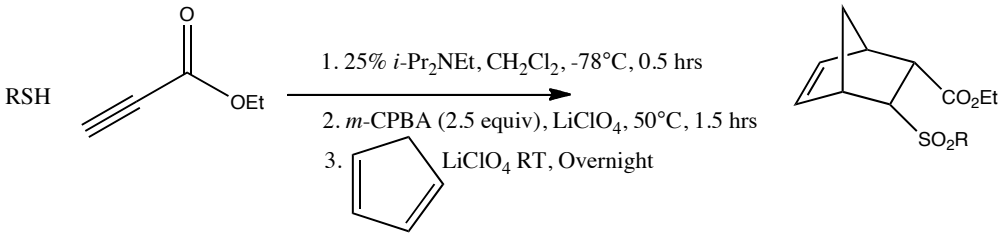


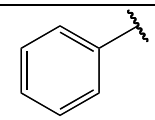
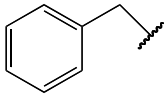
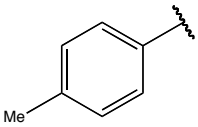
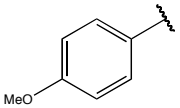
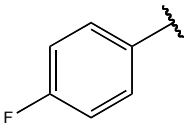
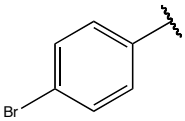
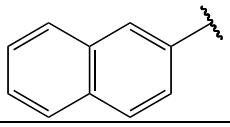
(2)

Finally, the full one-pot sequence was investigated and conducted on large scale (2.0 mmol). Low conversions proved to be an early obstacle for the one-pot sequence using the 4-fluorothiophenol and 4-bromothiophenol thiols as nucleophiles, and a variety of different Lewis acids and solvent conditions were investigated. It was discovered that using dichloroethane as solvent is crucial for the successful one-pot sequence with the bromo-substituted thiol as the nucleophile, so that the reactions could be heated to a higher temperature to achieve more efficient conversion. Ultimately, the addition of 1.0 equivalent of $LiClO_4$ at the oxidation step and an *additional* 1.0 equivalent of $LiClO_4$ added at the Diels–Alder step of the one-pot sequence yielded complete conversion to the Diels–Alder product for both the 4-fluorothiophenol and 4-bromothiophenol thiol nucleophiles. This optimization of the one-pot sequence was applied to the remaining

thiol nucleophiles under investigation, and yields were obtained for the complete one-pot process, shown in Table 9.

Table 9. Final Yields of Diels–Alder Endo Products for Various Thiol Nucleophiles.[iii]

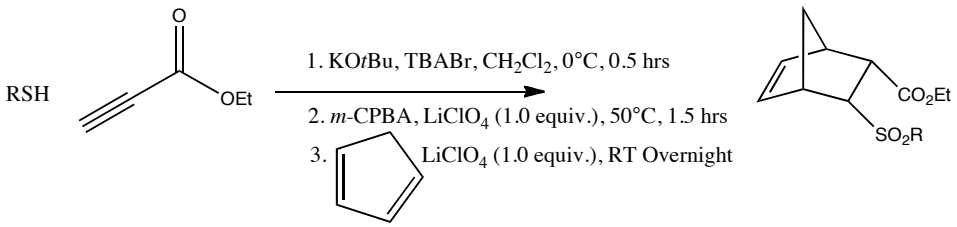


Thiol	$LiClO_4$ in Step 2 (equiv)	$LiClO_4$ in Step 3 (equiv)	Yield of Endo (%)	Product
	1.0	1.0	75	3b
	0.5	-	67	3c
	0.5	-	71	3d
	1.0	1.0	81	3e
	1.0	1.0	56	3f
	1.0	1.0	57*	3g
	1.0	1.0	60	3h

*Dichloroethane used as solvent.

[iii] Confirmation of the endo stereochemistry of the products was established by 2-D NOESY Homonuclear NMR experiments.

Because of the previously observed decomposition under normal oxidation conditions for the cyclohexanethiol nucleophile, an alternative procedure for the full three-step one-pot synthesis of the Diels–Alder product was developed to obtain a 47% yield of desired product, illustrated in Equation 3.



(3) Endo: 47% yield

One hypothesis for the disparity in endo product yields for the various thiol nucleophiles is that the rate of enoate isomerization from *Z* to *E* stereochemistry varies with the thiol. It is theorized that only the *Z* stereochemistry participates in the Diels–Alder step of the one-pot process to yield the desired endo product. Therefore, the difference in the ratio of *Z* to *E* isomers, as illustrated in Table 7 and Table 8, is largely reflected in the difference in obtained yields of the desired product. Electron-withdrawing groups on the aromatic ring are more likely to lead to attack by exogenous nucleophiles upon the double bond of the enoate. Attack by nucleophiles, such as residual diisopropylethylamine or deprotonated *m*-CPBA, result in a higher rate of isomerization from *Z* to *E* stereochemistry when the enoate is electron poor, decreasing the ratio of *Z* to *E* isomers and the overall yield of the desired product.

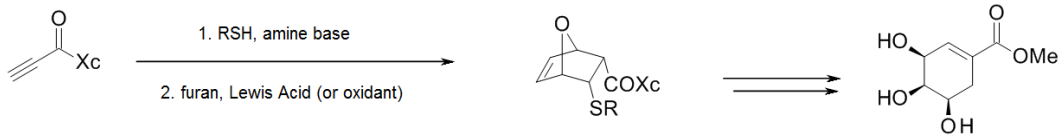
Therefore, it is hypothesized that the best yield is obtained for the full one-pot sequence of the methoxy-substituted thiol nucleophile because the methoxy substituent at the para position of the aromatic ring is an electron donor, and thus is more likely to donate electrons into the aromatic ring and pi system of the enoate. This property results in a slower rate of isomerization from *Z* to *E* stereochemistry, and in a higher final yield.

Thus, the original ratio of *Z* to *E* isomers and the subsequent rate of isomerization from *Z* to *E* will impact the final yield of the desired Diels–Alder product.

3. Conclusion and Future Research Efforts

With the success of optimizing the one-pot process for aromatic thiol nucleophiles, current work is being conducted on the use of alkyl thiols, such as dodecanethiol and octanethiol. The successful expansion to different dienes utilized in the Diels–Alder step of the one-pot synthesis would also increase the variety of complex cyclic products constructed using this method. In addition to exploring other substrates, future work will be aimed at utilizing a chiral catalyst in the place of $LiClO_4$ in the one-pot sequence to gain control of the resulting stereochemistry in the final products of the full one-pot process. The ability to control the stereochemistry of the final products would be valuable in the synthesis of specific, biologically active compounds.

Expansion of this reaction to utilize a wider variety of substrates and to control the stereochemistry of the final products should prove attractive to the pharmaceutical industry. This method could be used in the production of complex intermediates and precursors to biologically active molecules, such as Methyl-5-epi-Shikimate[7] or Deipeptyl-IV-Peptidase inhibitors,[8] as illustrated in Equation 4.



Synthesis of (+)-Methyl-5-epi-Shikimate **(4)**

References

1. For an example of a one-pot synthesis including a Diels–Alder reaction: Sow, B., Bellavance, G., Barabe, F., and Barriault, L. "One-pot Diels–Alder cycloaddition/gold(I)-catalyzed 6-*endo-dig* cyclization for the synthesis of the complex bicyclo[3.3.1]alkenone framework." *Beilstein J. Org. Chem.* **2011,** *7,* 1007–1013. doi:10.3762/bjoc.7.114

2. For an example of the enantioselective conjugate addition of thioamides and terminal alkynes: Yazaki, R, Kumagai, N., and Shibasaki, M. "Direct Catalytic Asymmetric Conjugate Addition of Terminal Alkynes to α,β-Unsaturated Thioamides." *J. Am. Chem. Soc.* **2010**, 132, 10275-10277.

3. For an example of the *Z* addition of a thiol to an ynoate with triethylamine: Maezaki, N., Yagi, S., Yoshigami, et al. "Pd-Catalyzed Slufinylzincation of Activated Alkynes with 1-Alkynyl Sulfoxides as a Sulfinyl Source," *J. Org. Chem.* **2003**, *68,* 5550-5558.

4. For an example of the enantioselective addition of thiols to aldehydes: Marigo, M., Schulte, T., Franzen, J., and Jorgensen, K. "Asymmetric Multicomponent Domino Reactions and Highly Enantioselective Conjugated Addition of Thiols to α,β-Unsaturated Aldehydes." *J. Am. Chem. Soc.* **2005**, *127*, 15710-15711.

5. Downey, C.W. *Synthesis of Chiral Carboxylic Acid Derivatives via Three-Component Coupling Reactions with Ynoate Electrophiles*. **2010**. ACS Report on Research.

6. Smaranda Craciun, Honors Thesis, University of Richmond, 2011.

7. For an example of synthesis of Methyl-5-epi-Shikimate: Sanchez-Abella, L., Fernandez, S., Armesto, N., Ferraro, M., and Gotor, V. "Novel and Efficient Syntheses of (–)-Methyl-4-epi-Shikimate and 4,5-Epoxy-Quinic and –Shikimic Acid Derivatives as Key Precursors to Prepare New Analogues." *J. Org. Chem.* **2006**, *71*, 5396-5399.

8. For an example of the synthesis of a deipeptyl IV peptidase inhibitor: Xu, F., Corley, E., Zacuto, M., et al. "Assymetric Synthesis of a Potent, Aminopiperidine-Fused Imidazopyridine Dipeptidyl Peptidase IV Inhibitor." *J. Org. Chem.* **2010**, *75*, 1343-1353.

Experimental

1. General Experimental Information:

All reactions were completed in oven-dried glassware and stirred using magnetic stir plates and stir bars. All reagents were used as obtained from the source except for cyclopentadiene which was distilled from dicyclopentadiene. To carry out all purification by column chromatography, silica gel (230-400 mesh) was used and compounds were separated by TLC and visualized using UV light or PMA stain if necessary (for cyclohexane thiol complete one-pot sequence only). All infrared spectra were recorded on an FT-IR spectrometer. All ^{1}H NMR spectra were recorded on a 500MHz spectrometer and reported in ppm using deuterated chloroform as an internal standard ($CDCl_3$ at 7.28 ppm). Data are reported using the following notation: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, coupling constants are in Hz. Proton decoupled ^{13}C NMR spectra were recorded using a 125 MHz spectrometer and are reported in ppm using deuterated chloroform as an internal standard ($CDCl_3$ at 77.0 ppm). High resolution mass spectra were obtained from electrospray ionization. Melting points were recorded using a capillary tube melting apparatus.

2. Experimental Procedures

General Experimental Procedure A: *Optimization of the addition of cyclohexadiene to the p-toluene thiol sulfone.*

To an oven-dried round bottomed flask under N_2, a p-toluene thiol-derived enoate (0.5 mmol) prepared using general experimental procedure C was added. Solvent (3.3 mL), Lewis acid (0.5 mmol) and cyclohexadiene (1.0 mmol) were added dropwise. The reaction was heated to reflux and allowed to run overnight. The reaction mixture was then passed through a silica plug with Et_2O and solvent was removed by rotary evaporation.

General Experimental Procedure B: *Heteroconjugate-Addition of different thiol nucleophiles to Ethyl Propiolate, produced compounds 1a-1h*

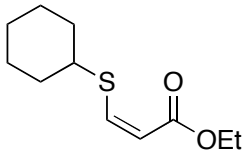
To an oven-dried round bottomed flask under N_2, thiol (2.0 mmol), CH_2Cl_2 (3.3 mL), and diisopropylethylamine (87 μL, 0.5mmol) were added and the reaction vessel was placed in a dry ice/acetone bath to stir for 10 minutes at -78 °C. Ethyl propiolate (203 μL, 2.0 mmol) was added dropwise and the reaction stirred for 30 minutes. The reaction mixture was passed through a column of silica with Et_2O, solvent was removed by rotary evaporation, and the compound was purified by column chromatography (5-25% EtOAc/hexanes).

General Experimental Procedure C: *Heterconjugate-Addition-Oxidation Reaction, produced compounds 2b-2h*

To an oven-dried round bottomed flask under N_2, thiol (2.0 mmol), CH_2Cl_2 (3.3 mL) and diisopropylethylamine (87 μL, 0.5 mmol) were added and the reaction vessel was placed in a dry ice/acetone bath to stir for 10 minutes at -78 °C. Ethyl propiolate (203 μL, 2.0 mmol) was added dropwise and the reaction stirred for 30 minutes. The reaction was removed from the dry ice/acetone bath, allowed to reach room temperature in a water bath, and one equivalent $LiClO_4$ (213 mg, 2.0 mmol) was added. An additional 13.3 mL of CH_2Cl_2 and mCPBA (1121 mg, 5.0 mmol, 77% pure) was added. The reaction was heated to reflux at 40 °C for 1.5 hours in an oil bath. The reaction was removed from the oil bath and allowed to reach room temperature. The reaction mixture was diluted with 40 mL Et_2O. An aqueous extraction was performed with 20 mL 1 M NaOH solution (2x), 20 mL 1 M HCl solution (1x), 20 mL 1 M $Na_2S_2O_3$ solution (1x), and 20 mL water (1x) and the organic layer was collected and dried over $MgSO_4$. The drying reagent was removed by vacuum filtration, solvent removed by rotary evaporation, and the resulting product was purified by column chromatography (5-25% EtOAc:hexanes).

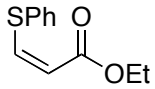
General Experimental Procedure D: *Full One-Pot Sequence, produced compounds 3b-3h*

To an oven-dried round bottomed flask under N_2, thiol (2.0 mmol), CH_2Cl_2 (3.3 mL) and diisopropylethylamine (87 μL, 0.5 mmol) were added and the reaction vessel was placed in a dry ice/acetone bath to stir for 10 minutes at -78 °C. Ethyl propiolate (203 μL, 2.0 mmol) was added dropwise and the reaction stirred for 30 minutes. The reaction was removed from the dry ice/acetone bath, allowed to reach room temperature in a water bath, and one equivalent $LiClO_4$ (213 mg, 2.0 mmol) was added. An additional 13.3 mL of CH_2Cl_2 and mCPBA (1121 mg, 5.0 mmol, 77% pure) was added. The reaction was heated to reflux at 50 °C for 1.5 hours in an oil bath. The reaction was removed from the oil bath, allowed to reach room temperature, and a second equivalent of $LiClO_4$ (213 mg, 2.0 mmol) was added. Cyclopentadiene (330 μL, 4.0 mmol) was added dropwise, and the reaction was capped and stirred overnight at room temperature. The reaction mixture was diluted with 40 mL Et_2O. An aqueous extraction was performed with 20 mL 1 M NaOH solution (2x), 20 mL 1 M HCl solution (1x), 20mL 1 M $Na_2S_2O_3$ solution (1x), and 20 mL water (1x) and the organic layer was collected and dried over $MgSO_4$. The drying agent was removed by vacuum filtration, solvent removed by rotary evaporation, and the resulting product was purified by column chromatography (5-35% EtOAc:hexanes).



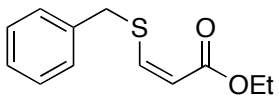
Ethyl 3-(cyclohexylthio)acrylate (1a)

White solid (45% yield) IR (film) 2927, 2847, 1695, 1565, 1441, 1372, 1200, 1157, 1032, 951, 797 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{11}H_{18}O_2SNa$ $[M+Na]^+$, 237.0925. Found 237.0916. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 10.3 Hz, 1H), 5.84 (d, *J* = 10.4 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.85 (ap tt, *J* = 11.0, 4.1 Hz, 1H), 2.08-2.01 (m, 2H), 1.85-1.80 (m, 2H), 1.68-1.62 (m, 1H), 1.50-1.45 (m, 2H), 1.41-1.34 (m, 2H), 1.30-1.26 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 148.3, 112.6, 60.0, 47.6, 33.6, 25.9, 25.4, 14.4; ***E* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 15.4 Hz, 1H), 5.82 (d, *J* = 15.4 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.09 (ap tt, *J* = 10.3, 3.8 Hz, 1H), 2.08-2.01 (m, 2H), 1.86-1.77 (m, 2H), 1.68-1.62 (m, 1H), 1.52-1.42 (m, 2H), 1.41-1.32 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 127-1.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 146.3, 114.2, 60.1, 45.0, 33.1, 25.8, 25.5, 14.3.



Ethyl 3-(phenylthio)acrylate (1b)

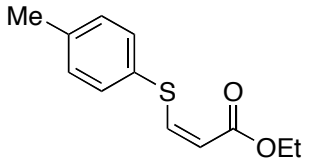
white solid (99% yield): IR (film) 3052, 2974, 1691, 1563, 1362, 1206, 1156 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{11}H_{12}O_2SNa$ $[M+Na]^+$, 231.0456. Found: 231.0464. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.42-7.36 (m, 3H), 7.28 (d, *J* = 10 Hz, 1H), 5.93 (d, *J* = 10.3 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 149.7, 131.1, 129.3, 128.2, 113.4, 60.3, 14.4; ***E* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 15.2 Hz, 1H), 7.52-7.49 (m, 2H), 7.45-7.28 (m, 3H), 5.68 (d, *J* = 15.3 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 146.8, 136.2, 133.0, 129.7, 129.1, 115.7, 60.3, 14.3.



Ethyl 3-(benzylthio)acrylate (1c)

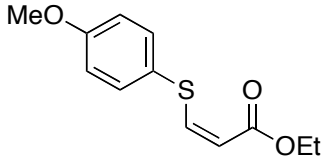
solid (79% yield): IR (film) 3056, 3029, 2975, 2924, 2913, 1693, 1561, 1495, 1456, 1204, 1153, 1033, 948 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{12}H_{14}O_2SNa$ $[M+Na]^+$, 245.0612. Found 245.0615. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H),

7.31-7.26 (m, 1H), 7.07 (d, *J* = 10.4 Hz, 1H), 5.83 (d, *J* = 10.0 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6; 148.5, 137.2, 129.0, 128.8, 127.5, 113.7, 60.1, 39.5, 14.4; ***E* isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 15.2 Hz, 1H), 7.37-7.33 (m, 4H), 7.32-7.27 (m, 1H), 5.83 (d, *J* = 15.4 Hz, 1H), 4.19 (q, *J* = 7.4 Hz, 2H), 4.04 (s, 2 H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 145.9, 135.6, 128.9, 128.8, 127.7, 114.6, 60.2, 36.6, 14.3.



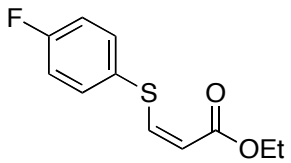
Ethyl 3-(*p*-tolylthio)acrylate (1d)

white solid (87% yield): IR (film) 3017, 2974, 2916, 2858, 1697, 1569, 1487, 1367, 1204, 1153, 1025, 940 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{12}H_{14}O_2SNa$ $[M+Na]^+$, 245.0612. Found 261.0621**. *Z* isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 10 Hz, 1H); 7.18 (d, *J* = 7.9 Hz, 2H), 5.89 (d, *J* = 9.9 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 150.5, 138.4, 133.3, 131.3, 130.1, 113.1, 60.3, 21.1, 14.4; ***E* isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 15.0 Hz, 1H), 7.37 (d, *J* = 6.5 Hz, 2H), 7.22 (d, *J* = 6.5 Hz, 2H), 5.60 (d, *J* = 15 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 147.5, 139.6, 132.3, 130.5, 126.7, 115.2, 60.2, 21.2, 14.3.



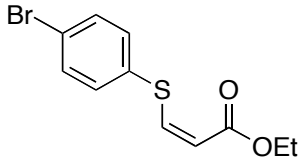
Ethyl 3-((4-methoxyphenyl)thio)acrylate (1e)

solid (80% yield): IR (film) 2972, 1692, 1592, 1566, 1492, 1287, 1245, 1206, 1157, 1027, 828, 797, 701 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{12}H_{14}O_3SNa$ $[M+Na]^+$, 261.0561. Found 261.0563. ***Z* isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.43 (m, 2H), 7.19 (d, *J* = 10.3 Hz, 1H), 6.93-6.90 (m, 2H), 5.86 (d, *J* = 10.0 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6; 160.1, 151.6, 133.5, 126.9, 114.9, 112.7, 60.3, 55.4, 14.4; ***E* isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 15.1 Hz, 1H), 7.44-7.41 (m, 2H), 6.97-6.95 (m, 2H), 5.52 (d, *J* = 14.7 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 2 H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) peaks below detection limit.



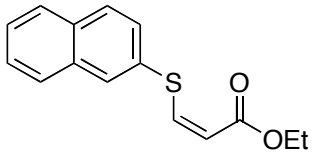
Ethyl 3-((4-fluorophenyl)thio)acrylate (1f)

white solid (91% yield): IR (film) 2982, 1693, 1591, 1569, 1489, 1397, 1264, 1165, 1154, 1091, 1029, 831, 797, 647 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{11}H_{11}O_2SFNa$ $[M+Na]^+$, 249.0362. Found 249.0373. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.18 (d, *J* = 10.0 Hz, 1H), 7.11-7.07 (m, 2H), 5.92 (d, *J* = 10.0 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 162.9 (d, *J* = 248.6 Hz), 150.0, 133.6 (d, *J* = 7.7 Hz), 131.5 (d, *J* = 2.9 Hz), 116.5 (d, *J* = 22.1 Hz), 113.5, 60.4, 14.3; ***E* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 15.0 Hz, 1H), 7.52-7.48 (m, 2H), 7.16-7.12 (m, 2H), 5.59 (d, *J* = 15.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) peaks below detection limit.



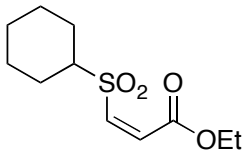
Ethyl 3-((4-bromophenyl)thio)acrylate (1g)

(80% yield): mp: 43-49 °C; IR (film) 2979, 2928, 1689, 1581, 1473, 1386, 1371, 1229, 1185, 1173, 1055, 1033, 1007, 829, 817, 798 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{11}H_{11}O_2SBrNa$ $[M+Na]^+$, 308.9561, 310.9540. Found 308.9553, 310.9528. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.33-7.31 (m, 2H), 7.16 (d, *J* = 10.0 Hz, 1H), 5.91 (d, *J* = 10.0 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 148.5, 135.3, 132.5, 132.4, 122.5, 114.0, 60.4, 14.4; ***E* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 15.0 Hz, 1H), 7.52-7.48 (m, 2H), 7.32-7.28 (m, 2H), 5.64 (d, *J* = 15.0 Hz, 1H), 4.14 (q, *J* = 6.9 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) peaks below detection limit.



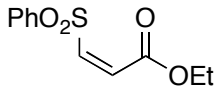
Ethyl 3-(naphthalen-2-ylthio)acrylate (1h)

(66% yield): mp: 34-37 °C IR (film) 2981, 2928, 1696, 1567, 1371, 1213, 1165, 1133, 1033, 799, 746, 668 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{15}H_{14}O_2SNa$ $[M+Na]^+$, 281.0612. Found 281.0625. ***Z* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (bs, 1H), 7.90-7.80 (m, 3H), 7.58-7.52 (m, 3H), 7.39 (d, *J* = 10.0 Hz, 1H), 5.99 (d, *J* = 10.0 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 149.5, 133.6, 133.4, 132.7, 130.2, 129.2, 128.2, 127.8, 127.6, 127.0, 126.8, 113.7, 60.4, 14.4; ***E* isomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (bs, 1H), 7.86-7.79 (m, 3H), 7.76-7.72 (m, 1H), 7.64 (dd, *J* = 1.9, 8.4 Hz, 1H), 7.50-7.44 (m, 2H), 5.72 (d, *J* = 15.1 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) peaks below detection limit.



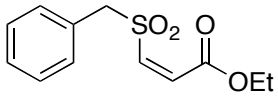
Ethyl 3-(cyclohexylsulfonyl)acrylate (2a)

solid (45% yield): mp: 42-45 ^{o}C; IR (film) 2932, 2856, 1733, 1308, 1231, 1126, 1112, 1021, 769, 726, 602 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, J = 11.8 Hz, 1H), 6.52 (d, J = 11.6 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.15 (apt t, J = 3.5, 12.2 Hz, 1H), 2.21-2.14 (m, 2H), 1.98-1.92 (m, 2H), 1.77-1.72 (m, 1H), 1.61-1.51 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.37-1.19 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 134.8, 133.4, 62.9, 62.1, 25.1, 25.0, 24.9, 13.9; HRMS (ESI): Exact mass calcd for $C_{11}H_{18}O_4SNa$ $[M+Na]^+$, 269.0824. Found 269.0817.



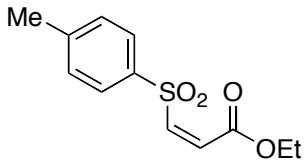
Ethyl 3-(phenylsulfonyl)acrylate (2b)

white solid (99% yield): mp: 69-71 ^{o}C; IR (film) 3052, 3031, 2986, 1727, 1628, 1584, 1452, 1234, 1147 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04-8.01 (m, 2H), 7.70-7.66 (m, 1H), 7.61-7.57 (m, 2H), 6.56 (d, J = 11.4 Hz, 1H), 6.52 (d, J = 11.6 Hz, 1H), 4.39 (q, J = 7.3 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 139.6, 135.2, 134.0, 131.9, 129.3, 128.3, 62.2, 14.0; HRMS (ESI): Exact mass calcd for $C_{11}H_{12}O_4SNa$ $[M+Na]^+$, 263.0354. Found 263.0348.



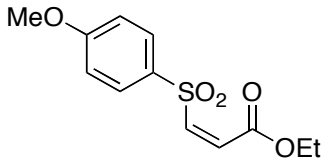
Ethyl 3-(benzylsulfonyl)acrylate (2c)

solid (79% yield). mp: 44-46 ^{o}C; IR (film) 3056, 3033, 2979, 2916, 2843, 1724, 1619, 1448, 1313, 1215, 1111, 1014 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.39 (m, 5H), 6.58 (d, J = 11.8 Hz, 1H), 6.38 (d, J = 11.5 Hz, 1H), 4.54 (s, 2H), 4.36 (q, J = 7.3 Hz, 2H), 1.38 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 136.3, 134.5, 131.1, 129.1, 129.0, 127.2, 62.3, 62.0, 14.0; HRMS (ESI): Exact mass calcd for $C_{12}H_{14}O_4SNa$ $[M+Na]^+$, 277.0511. Found 277.0512.



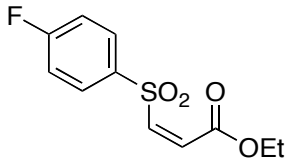
Ethyl 3-tosylacrylate (2d)

white solid (87% yield): mp: 36-38 ^{o}C; IR (film) 3048, 2979, 2916, 1728, 1623, 1592, 1309,1227, 1138, 1091, 1010, 812 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.9 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 6.53 (d, *J* = 11.6 Hz, 1H), 6.48 (d, *J* = 11.5 Hz, 1H), 4.36 (q, *J* = 7.3 Hz, 2H), 2.45 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 145.2, 136.6, 135.4, 131.5, 130.0, 128.3, 62.1, 21.7, 14.0; HRMS (ESI): Exact mass calcd for $C_{12}H_{14}O_4SNa$ $[M+Na]^+$, 277.0511. Found 277.0519.



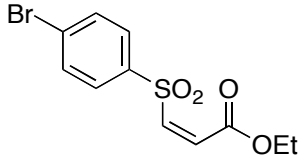
Ethyl 3-((4-methoxyphenyl)sulfonyl)acrylate (2e)

solid (80% yield): mp: 74-77 ^{o}C; IR (film) 2977, 2841, 1734, 1682, 1595, 1577, 1498, 1301, 1260, 1144, 1087, 1022, 833, 805, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 6.99-6.96 (m, 2H), 6.49 (d, *J* = 11.6 Hz, 1H), 6.43 (d, *J* = 11.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 164.1, 135.5, 130.8, 130.5, 114.6, 62.0, 55.8, 14.0; HRMS (ESI): Exact mass calcd for $C_{12}H_{14}O_5SNa$ $[M+Na]^+$, 293.0460. Found 293.0461.



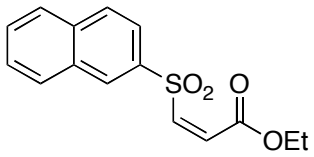
Ethyl 3-((4-fluorophenyl)sulfonyl)acrylate (2f)

white solid (91% yield): mp: 52-53 ^{o}C; IR (film) 3047, 2984, 1726, 1623, 1588, 1494, 1339, 1231, 1143, 1024, 970, 840, 741, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07-8.03 (m, 2H), 7.29-7.23 (m, 2H), 6.55 (d, *J* = 11.5 Hz, 1H), 6.53 (d, *J* = 11.9 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, (d, *J* = 256.2 Hz), 163.9, 135.6 (d, *J* = 2.9 Hz), 135.1, 132.3, 131.2 (d, *J* = 9.6 Hz), 116.6 (d, *J* = 31.6 Hz), 62.2, 13.9; HRMS (ESI): Exact mass calcd for $C_{11}H_{11}O_4SFNa$ $[M+Na]^+$, 281.0260. Found 281.0265.



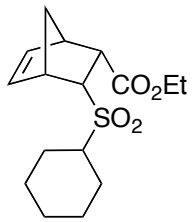
Ethyl 3-((4-bromophenyl)sulfonyl)acrylate (2g)

White solid (80% yield): mp: 55-57 ^{o}C; IR (film) 3029, 1721, 1571, 1368, 1315, 1241, 1145, 1065, 1009, 818, 765, 743, 720, 617 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90-7.87 (m, 2H), 7.74-7.71 (m, 2H), 6.56 (d, *J* = 11.6 Hz, 1H), 6.53 (d, *J* = 11.5 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 138.6, 135.0, 132.7, 132.6, 129.8, 129.5, 62.3, 14.0. Spectrum includes an unassigned peak at 120.0; HRMS (ESI): Exact mass calcd for $C_{11}H_{11}O_4SBrNa$ $[M+Na]^+$, 340.9459, 342.9439. Found 340.9463, 342.9431**.**



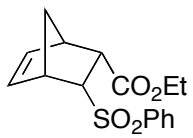
Ethyl 3-(naphthalen-2-ylsulfonyl)acrylate (2h)

(66% yield): mp: 40-42 ^{o}C; IR (film) 2904, 1736, 1369, 1237, 1150, 1021, 860, 750, 619 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (bs, 1H), 8.05-7.99 (m, 3H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.73-7.64 (m, 2H), 6.61 (d, *J* = 11.6 Hz, 1H), 6.55 (d, *J* = 11.6 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 136.3, 135.5, 135.2, 132.2, 131.9, 130.2, 129.7, 129.6, 129.5, 128.0, 127.7, 122.7, 62.2, 14.0; HRMS (ESI): Exact mass calcd for $C_{15}H_{14}O_4SNa$ $[M+Na]^+$, 313.0511. Found 313.0511.



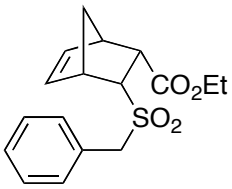
***cis*,*endo*-Ethyl 3-(cyclohexylsulfonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (3a)**

(47% yield): mp: 75-78°C; IR (film) 2910, 2841, 1745, 1292, 1239, 1188, 1118, 1042, 1026, 732, 669 cm^{-1}**;** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (dd, J=2.8, 5.3 Hz, 1H), 6.32 (dd, J= 2.9, 5.4 Hz, 1H), 4.19 (dq, J=7.2, 11 Hz, 1H), 4.11-4.03 (m, 2H), 3.44 (bs, 1H), 3.36 (dd, J=3.1, 10, 2H), 3.25-3.24 (m, 2H), 2.18-2.10 (m, 2H), 1.98-1.90 (m, 2H), 1.75-1.70 (m, 1H), 1.64 (dq, J=3.5, 12.5 Hz, 1H), 1.54-1.45 (m, 1H), 1.40-1.19 (m, 4H), 1.27 (t, J=7.2 Hz 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.55, 137.37, 133.01, 129.7, 77.19, 61.79, 60.95, 49.14, 47.63, 46.27, 26.67, 25.18, 23.12, 13.93; HRMS (ESI): Exact mass calcd for $C_{16}H_{24}O_4SNa$ $[M^+Na]^+$, TBD



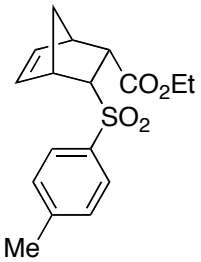
***cis*,*endo*-Ethyl 3-(phenylsulfonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (3b)**

(75% yield): mp: 75-80 °C; IR (film) 2980, 1735, 1446, 1321, 1246, 1144, 1086, 750, 691 cm^{-1}**;** ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 2H), 6.62 (dd, *J* = 3.1, 5.6 Hz, 1H), 6.28 (dd, *J* = 2.8, 5.3 Hz, 1H), 4.29-4.22 (m, 1H), 4.19-4.12 (m, 2H), 3.47 (dd, *J* = 3.2, 10.0 Hz, 1H), 3.25 (s, 1H), 2.95 (s, 1H), 1.51-1.48 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.28 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 141.3, 137.7, 133.4, 131.9, 129.1, 127.9, 69.2, 61.0, 49.4, 48.2, 47.1, 46.7, 13.9; HRMS (ESI): Exact mass calcd for $C_{16}H_{18}O_4SNa$ $[M+Na]^+$, 329.0824. Found 329.0822.



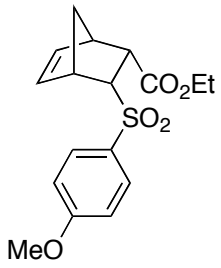
***cis*,*endo*-Ethyl 3-(benzylsulfonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (3c)**

(67% yield): mp: 47-50 °C; IR (film) 3061, 2977, 2881, 1736, 1596, 1568, 1493, 1314, 1177, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.45-7.39 (m, 3H), 6.51 (dd, *J* = 3.1, 2.5 Hz, 1H), 6.32 (dd, *J* = 2.9, 2.7 Hz, 1H), 4.65 (d, *J* = 13.6 Hz, 1H), 4.33-4.26 (m, 2H), 4.24-4.16 (m, 1H), 3.78 (dd, *J* = 3.3, 6.5 Hz, 1H), 3.36 (dd, *J* = 3.0, 6.9 Hz, 1H), 3.35 (s, 1H), 3.26 (s, 1H), 1.48 (td, *J* = 9.0, 1.8 Hz, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.21 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 137.3, 132.6, 130.8, 129.0, 128.95, 128.87, 62.9, 61.4, 61.2, 49.3, 47.8, 46.2, 46.0, 14.1; HRMS (ESI): Exact mass calcd for $C_{17}H_{20}O_4SNa$ $[M+Na]^+$, 343.0980. Found 343.0985.



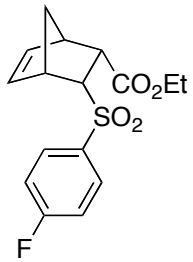
***cis*,*endo*-Ethyl 3-tosylbicyclo[2.2.1]hept-5-ene-2-carboxylate (3d)**

(71% yield) mp: 98-100 °C; IR (film) 3060, 2974, 2869, 1728, 1592, 1316, 1238, 1133, 733, 648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.60 (dd, *J* = 3.3, 1.5 Hz, 1H), 6.25 (dd, *J* = 2.8, 3.0 Hz, 1H), 4.18 (qd, *J* = 7.3, 7.2 Hz, 2H), 4.10 (dd, *J* = 3.2, 6.9 Hz, 1H), 3.45 (dd, *J* = 6.9, 3.0 Hz, 1H), 3.22 (s, 1H), 2.92 (s, 1H), 2.45 (s, 3 H), 1.46 (dt, *J* = 8.6, 1.9 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 144.3, 138.4, 137.7, 131.9, 129.7, 128.1, 69.4, 61.1, 49.3, 48.2, 47.1, 46.7, 21.6, 13.9; HRMS (ESI) exact mass calcd for $C_{17}H_{20}O_4SNa$ $[M+Na]^+$, 343.0980. Found 343.0974.



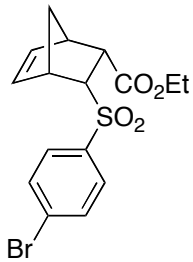
***cis*,*endo*-Ethyl 3-((4-methoxyphenyl)sulfonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (3e)**

(81% yield): mp: 128-130 °C; IR (film) 2980, 1732, 1594, 1498, 1322, 1259, 1140, 1025, 837, 803, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83-7.80 (m, 2H), 7.03-7.00 (m, 2H), 6.58 (dd, *J* = 2.8, 5.3 Hz, 1H), 6.22 (dd, *J* = 2.8, 5.3 Hz, 1H), 4.22 (dq, *J* = 10.6, 7.2 Hz, 1H), 4.14 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.09 (dd, *J* = 3.1, 10.0 Hz, 1H), 3.88 (s, 3H), 3.44 (dd, *J* = 3.1, 10.0 Hz, 1H), 3.21 (s, 1H), 2.90 (s, 1H), 1.45 (dt, *J* = 8.8, 1.9 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 163.5, 139.7, 132.9, 131.9, 130.2, 114.2, 69.7, 61.1, 55.7, 49.3, 48.2, 47.1, 46.7, 13.9; HRMS (ESI): Exact mass calcd for $C_{17}H_{20}O_5SNa$ $[M+Na]^+$, 359.0929. Found 359.0927.



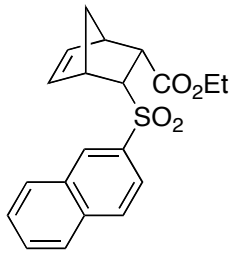
***cis*,*endo*-Ethyl 3-((4-fluorophenyl)sulfonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (3f)**

(56% yield) mp: 103 °C; IR (film) 2977, 1736, 1590, 1494, 1325, 1290, 1237, 1185, 1143, 1084, 842, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96-7.92 (m, 2H), 7.29-7.22 (m, 2H), 6.60 (dd, *J* = 2.8, 5.3 Hz, 1H), 6.25 (dd, *J* = 2.8, 5.6 Hz, 1H), 4.24 (dq, *J* = 11.0, 7.2 Hz, 1H), 4.14 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.11 (dd, *J* = 3.1, 10.0 Hz, 1H), 3.46 (dd, *J* = 3.1, 10.0 Hz, 1H), 3.25 (s, 1H), 3.00 (s, 1H), 1.50 (dt, *J* = 8.8, 1.9 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.30-1.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 165.5 (d, *J* = 256.3 Hz), 137.9, 137.4 (d, *J* = 3.8 Hz), 131.8, 130.9 (d, *J* = 9.6 Hz), 116.3 (d, *J* = 22.1), 69.6, 61.2, 49.5, 48.2, 47.1, 46.7, 13.9; HRMS (ESI): Exact mass calcd for $C_{16}H_{17}O_4SFNa$ $[M+Na]^+$, 347.0729. Found 347.0741.



***cis*,*endo*-Ethyl 3-((4-bromophenyl)sulfonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (3g)**

(57% yield): mp:45-50 °C; IR (film) 2974, 1733, 1574, 1473, 1323, 1276, 1185, 1144, 1084, 1010, 827, 757, 609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81-7.77 (m, 2H), 7.74-7.70 (m, 2H), 6.60 (dd, *J* = 3.2, 5.7 Hz, 1H), 6.26 (dd, *J* = 2.8, 5.6 Hz, 1H), 4.24 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.14 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.11 (dd, *J* = 3.1, 10.0 Hz, 1H), 3.46 (dd, *J* = 3.1, 10.0 Hz, 1H), 3.26 (s, 1H), 3.03 (s, 1H), 1.51 (dt, *J* = 9.1, 1.9 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.30-1.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 140.4, 137.9, 132.4, 131.8, 129.6, 128.6, 69.4, 61.2, 49.5, 48.2, 47.1, 46.7, 14.0; HRMS (ESI): Exact mass calcd for $C_{16}H_{17}O_4SBrNa$ $[M+Na]^+$, 406.9929, 408.9908. Found 406.9916, 408.9894.



***cis*,*endo*-Ethyl 3-(naphthalen-2-ylsulfonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (3h)**

(60% yield): mp: 138-140°C; IR (film) 2984, 2936, 2360, 2342, 1736, 1369, 1320, 1246, 1190, 1128, 1072, 875, 754, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.47 (bs, 1H), 8.04-8.00 (m, 2H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.93 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.71-7.63 (m, 2H), 6.65 (dd, *J* = 3.1, 5.6 Hz, 1H), 6.33 (dd, *J* = 2.8, 5.6 Hz, 1H), 4.28 (dq, *J* = 10.6, 6.9 Hz, 1H), 4.24 (dd, *J* = 3.1, 10.0 Hz, 1H), 4.17 (dq, *J* = 10.6, 7.2 Hz, 1H), 3.50 (dd, *J* = 3.2, 10.0 Hz, 1H), 3.26 (s, 1H), 2.96 (s, 1H), 1.48 (dt, *J* = 9.1, 1.9 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.30-1.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 138.2, 137.8, 135.2, 132.2, 132.0, 129.6, 129.5, 129.4, 129.2, 128.0, 127.6, 122.9, 69.4, 61.2, 49.5, 48.2, 47.1, 46.8, 14.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{20}O_4SNa$ $[M+Na]^+$, 379.0980. Found 379.0987.

3. List of Tables:

4. List of Abbreviations:

E	Entgegen
*m*CPBA	meta-chloroperbenzoic acid
NOESY	Nuclear Overhauser Effect Spectroscopy
NMR	Nuclear Magnetic Resonance
p	para
Z	Zusammen
TBABr	Tetrabutyl Ammonium Bromide